

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:  
JOHN P. WHITE  
COOPER & DUNHAM LLP  
1185 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036

Date of mailing  
(day/month/year)

18 JUN 2008

Applicant's or agent's file reference  
75615-PCT/JPW/BB

## FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 08/02472

International filing date (day/month/year)

25 February 2008 (25.02.2008)

Priority date (day/month/year)

26 February 2007 (26.02.2007)

International Patent Classification (IPC) or both national classification and IPC  
IPC(8) - A01N 43/40; A61K 31/44 (2008.04) (2008.04)

USPC - 514/358

Applicant TEVA PHARMACEUTICAL INDUSTRIES, LTD.

## 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

## 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

## 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US  
Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450  
Facsimile No. 571-273-3201

Date of completion of this opinion

17 May 2008 (17.05.2008)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300  
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

Applicants: Meir Shinitzky et al.  
Serial No.: 10/530,776  
Filed: December 19, 2005  
Exhibit 14

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/02472

## Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into \_\_\_\_\_ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
- a. type of material
- ☐ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ on paper
- ☐ in electronic form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☐ filed together with the international application in electronic form
- ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/02472

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 5-6 and 10-14

because:

☐ the said international application, or the said claims Nos. \_\_\_\_\_ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5-6 and 10-14 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 5-6 and 10-14 are improper multiple dependent claims as they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 5-6 and 10-14

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE  
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International application No.

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Box No. V	Reasoned statement under Rule 43b1s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																								
<p>1. Statement</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td rowspan="2" style="width: 30%; vertical-align: top;">Novelty (N)</td> <td style="width: 10%;">Claims</td> <td style="width: 40%; border-bottom: 1px solid black;">1-4, 7-9 and 15</td> <td style="width: 20%; text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td style="border-bottom: 1px solid black;">NONE</td> <td style="text-align: right;">NO</td> </tr> <tr> <td rowspan="2" style="vertical-align: top;">Inventive step (IS)</td> <td>Claims</td> <td style="border-bottom: 1px solid black;">NONE</td> <td style="text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td style="border-bottom: 1px solid black;">1-4, 7-9 and 15</td> <td style="text-align: right;">NO</td> </tr> <tr> <td rowspan="2" style="vertical-align: top;">Industrial applicability (IA)</td> <td>Claims</td> <td style="border-bottom: 1px solid black;">1-4, 7-9 and 15</td> <td style="text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td style="border-bottom: 1px solid black;">NONE</td> <td style="text-align: right;">NO</td> </tr> </table>					Novelty (N)	Claims	1-4, 7-9 and 15	YES	Claims	NONE	NO	Inventive step (IS)	Claims	NONE	YES	Claims	1-4, 7-9 and 15	NO	Industrial applicability (IA)	Claims	1-4, 7-9 and 15	YES	Claims	NONE	NO
Novelty (N)	Claims	1-4, 7-9 and 15	YES																						
	Claims	NONE	NO																						
Inventive step (IS)	Claims	NONE	YES																						
	Claims	1-4, 7-9 and 15	NO																						
Industrial applicability (IA)	Claims	1-4, 7-9 and 15	YES																						
	Claims	NONE	NO																						
<p>2. Citations and explanations:</p> <p>Claims 1-4, 7-9 and 15 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0173053 A1 to Shinitzky et al. (hereinafter 'Shinitzky') in view of US 6,458,772 B1 to Zhou et al. (hereinafter 'Zhou').</p> <p>Regarding claim 1, Shinitzky teaches amino-phenyl-acetic acid octadec-9-(Z)-enyl ester (para [0157], [0060]-[0062] in general). Shinitzky differs from the instant claim regarding a teaching of an enantiopure compound. Zhou teaches enantiopure (col 4, in 40-45) fatty alcohol esters (col 3, in 40-45). A person having ordinary skill in the art would have been motivated to modify (or to further modify) the compound of Shinitzky in accordance with the teachings of Zhou such an enantiopure amino-phenyl-acetic acid octadec-9-(Z)-enyl ester would have been obvious since Shinitzky teaches starting components that are racemically active or preferred (para [0084]). Moreover, enantiomerically pure compounds would have been obvious to one of ordinary skill in the art over such purity requirements in common drugs such as ibuprofen.</p> <p>Regarding claim 2, as in claim 1, Zhou further teaches enantiopure (col 4, in 40-45) fatty alcohol esters (col 3, in 40-45).</p> <p>Regarding claims 3-4, as in claim 1, Zhou further teaches enantiopure (col 4, in 40-45) fatty alcohol esters (col 3, in 40-45), which would have made the (R) and (S) isomers obvious to one of ordinary skill in the art since alone they are the pure enantiomers.</p> <p>Regarding claim 7, as in claim 1, Shinitzky further teaches a method of preparing (para [0157]-[0158]) comprising heating (para [0158]) a mixture of oleyl alcohol (para [0037], [0084]) and a stereoisomer of phenylglycine (para [0040]) chloride (para [0109] which teaches salt forms thereby obviating such to one of ordinary skill in the art); and isolating the compound from the mixture (para [0158]).</p> <p>Regarding claims 8-9, as in claim 7, Shinitzky further teaches wherein the polar aprotic solvent is acetonitrile (para [0193]).</p> <p>Regarding claim 15, Zhou teaches a method of determining purity (col 4, in 40-45, since a measurement of purity is taught) comprising chromatographic means (col 20, in 40-50). Zhou does not specifically recite the claimed method, but such (i.e. determining the enantiomeric purity of a composition comprising amino-phenyl-acetic acid octadec-9-(Z)-enyl ester or a stereoisomer of amino-phenyl-acetic acid octadec-9-(Z)-enyl ester comprising a) analyzing the composition using chiral chromatography under suitable conditions; b) analyzing an enantiomerically pure stereoisomer of amino-phenyl-acetic acid octadec-9-(Z)-enyl ester using chiral chromatography under the same conditions as in step a; and c) comparing the chromatographic analyses of step a and step b, thereby determining the enantiomeric purity of the composition) would have been obvious to one of ordinary skill in the art as it would have been routine to one of ordinary skill in the art in view of the teaching in the reference for determining the percentage of the pure substance and the knowledge of one of ordinary skill knowing to make a comparison with a known.</p> <p>Claims 1-4, 7-9 and 15 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.</p>																									